which lacks a KS domain, so that the hybrid PKS gene encodes a hybrid extension module consisting of said KS domain of the first nucleic acid portion and said partial extension module.

Cancel claims 3, 24, 29, 45 and 46.

Marked-up versions of the amended specification page and claims 39, 50 and 52-54 are attached.

REMARKS

The May 21, 2002 Official Action and the references cited therein have been carefully considered. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the May 21, 2002 Official Action. The initial due date for response, therefore, was August 21, 2002. A petition for a three (3) month extension of the response period is presented with this Request for Continued Examination (RCE) and accompanying submission, in the form of an amendment and request for reconsideration, which are being filed within the three (3) month extension period.

The Examiner continues to rely on Khosla '290 as constituting evidence of lack of novelty and evidence of obviousness, alone and in combination with certain secondary references, with respect to a number of Applicants' claims. In this connection, the Examiner maintains that:

(i) Claims 1, 31-37 and 39 are allegedly anticipated by Khosla '290, under §102(e);

(ii) Claims 2, 3, 25 and 26 are allegedly unpatentable in view of Khosla '290, under §103(a); and

(iii) Claim 27 is allegedly unpatentable in view of the combined disclosures of Khosla '290 and Kao et al. under §103(a).

A majority of the new claims submitted in response to the preceding Official Action (Claims 44-58) also stand rejected under §102(a) as allegedly anticipated by Khosla '290 (Claims 47-49, 55-58), or under §103(a) as allegedly unpatentable in view of Khosla '290 considered alone (Claim 44), or in combination with newly-cited U.S. Patent 5,190,871 to Cox et al. (hereinafter "Cox") (Claim 51).

As for the rejections that are not prior art-based, the Examiner adheres to the position that the subject matter of Claims 29 and 39 is inadequately enabled by Applicants' specification, that Claim 29 lacks a written description in the specification, and that Claim 24 is allegedly indefinite for failing to particularly point out the subject matter which Applicants regard as the invention.

Additional §112, first paragraph, rejections have been entered against new Claims 45, 46, 50 and 52-54, which allegedly lack a written description in the specification. Claims 45 and 46 have also been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out the subject matter which Applicants regard as the invention. Claims 45, 46 and 52 are further rejected under 35 U.S.C. §132 as allegedly introducing new matter into this application.

The Examiner also advises Applicants that Claims 3 and 35, if allowed, will be objected to as substantial duplicates of Claims 44 and 47, respectively.

The informal nature of the drawings is again noted at page 2 of the May 21, 2002 Official Action. It is respectfully requested that the requirement for submission of formal drawings be held in abeyance, pending the indication of allowable subject matter. The same request is made regarding the informalities noted in paragraphs 38 and 39 of the May 21, 2002 Official Action, under the heading "Examiner Notes".

In accordance with the present amendments, the specification has been further amended by replacing the paragraph at page 63, lines 7-12, in order to eliminate the redundancy noted by the Examiner at page 11 of the May 21, 2002 Official Action.

Furthermore, claim 39 has been amended by characterizing the recited microorganism as an "actinomycete".

Support for this amendment is provided in the specification at page 16, lines 8-9.

Claims 50, 52 and 53 have been amended to delete the language which the Examiner deems objectionable. Support for the amendment of claim 50 is provided at page 9, lines 32-34. Support for the amendatory language of claim 52 is provided at page 16, lines 30-33 of the specification.

Claim 54 has been amended to better conform to the description of the invention provided at page 7, lines 29-35 of the specification.

Applicants are also presenting herewith new claims 59-63. Support for new claim 59 is provided in the present specification at page 16, lines 11-20. Support for new claim 60 is provided at page 18, line 5 of this specification. New claims 61-63 correspond essentially to claims 45, 46 and 24, respectively.

Claims 3, 24, 29, 45 and 46 have been canceled. The various rejections of claims 3, 24, 29, 45 and 46 are, therefore, rendered moot. Moreover, those grounds of rejection are inapplicable to the new claims submitted in place of claims 24, 45 and 46, i.e. claims 61-63. Claims 61-63 omit the terminology deemed objectionable in claims 24, 45 and 46.

No new matter has been introduced into this application by reason of any of the amendments presented herewith, as the amendments to claims 39, 52 and 54 and new claims 59-63 are fairly based on the specification as originally filed. Moreover,

none of the present claims amendments is believed to constitute a surrender of any originally claimed subject matter, or a narrowing of the claims in order to establish patentability. The effect of these amendments is merely to make express that which was implicit in the claims as originally worded.

For the reasons set forth below, applicants respectfully submit that each ground of rejection set forth in the May 21, 2002 Official Action either lacks merit or cannot be maintained in view of the present amendments, or both. Those grounds of rejection are, therefore, respectfully traversed.

A. Khosla '290 Fails to Provide Evidence of Unpatentability With Respect to Applicants' Hybrid PKS Gene

The Examiner's reliance on Khosla '290 is clearly misplaced, as this reference fails to provide evidence of unpatentability with respect to the hybrid PKS gene claimed by Applicants in this application.

In re Benno 226 U.S.P.Q. 683 (Fed. Cir. 1985), contrary to the Examiner's assessment, plainly establishes the impropriety of the prior art rejections based in whole or in part on Khosla '290, i.e., all of the prior art rejections included in the May 21, 2002 Official Action. In re Benno cannot be summarily dismissed on the basis that the Court's comments "are related to infringement", as the Examiner attempts to do in this case.

In re Benno stands for the proposition that it is error for the Patent and Trademark Office to reject a claim in a patent

application merely because the subject matter of the rejected claim falls within the broadly-worded claim of a prior art patent. See, D. Chisum, Chisum on Patents, §3.06[1][a] (2002). In re Benno involved an appeal from a final rejection of claims directed to a multi-package, e.g. a "six-pack", employing elastic, blown plastic film material. One of the issues on appeal was the propriety of a prior art rejection based on a patent to Danti. The Board of Appeals determined that claim 1 of the Danti patent was broad enough to read on a package having the features of Benno's claimed invention and, therefore, concluded that the claims were unpatentable in view of Danti. In reversing this ground of rejection, the Court stated: "[W]e hold that the board erred in relying on Danti's claim 1 in deciding that appellant's claims would have been obvious from that reference alone and also in reaching that conclusion.

The holding in In re Benno was followed in Corning Glass Works v. Sumitomo Electric U.S.A., Inc., 5 U.S.P.Q.2d 1545 (S.D.N.Y. 1987), *affd*. 9 U.S.P.Q.2d 1962 (Fed. Cir. 1989). In Corning Glass, the Court rejected as without merit a patent invalidity defense contending that the invention of the patent in suit was anticipated by the claims of a published Japanese patent application. In this connection, the Court stated: "A prior art patent (or published application) is a reference only for that which it teaches", citing In re Benno, and ultimately concluded that the Japanese application did not teach the claimed invention, even though its claims were broad enough to cover it.

It is evident from In re Benno and its progeny that a prior patent which incidentally claims an applicant's invention cannot anticipate that invention unless the prior patent contains a supporting disclosure in such detail as to teach a person of ordinary skill in the art how to make and use the applicant's invention. In other words, the scope of a patent's claim is no measure of what the patent discloses. Rather, a patent discloses only that which it actually describes. Thus, the Examiner is unquestionably in error when asserting in the final rejection (and in the preceding Official Action) that Khosla '290 provides anticipatory "teachings", but primarily citing certain claims of Khosla '290 as constituting such "teachings". This is clearly improper in view of In re Benno.

Apart from the claims of Khosla '290, the Examiner cites various disparate passages of the specification of this reference in support of the final rejection. However, the cited passages do not provide the identical disclosure or description of Applicants' claimed invention that it is a prerequisite of an allegedly anticipatory prior art reference. In re Arkley, 172 U.S.P.Q. 524(C.C.P.A. 1972). Regarding the examples of genes for use in hybrid modular PKS clusters, the Examiner is apparently referring to erythromycin, tylosin, carbomycin, spiramycin, avermectin and rifamycin, as disclosed at column 15, lines 12-14 of Khosla '290. However, this listing of PKS clusters from which genes may purportedly be derived to produce hybrid replacement clusters includes typeI, II and fungal types. This plainly does

not constitute an identical disclosure or description of Applicants' typeI/typeI hybrids.

The Examiner cites column 19, lines 38-40 of Khosla '290 as partial support for the alleged teaching of Applicant's claimed DNA molecule operably linked to an actinorhodin (act) promoter in the presence of "act II-ORF 4, an activator gene, which is required for transcription from these [actI/actIII] promoters". However, the cited passage from the specification of Khosla '290 concerns techniques for cloning ery genes as "described in Example 7 and summarized in Figure 10" (column 20, lines 11-12). A review of Example 7 readily reveals that it provides no teaching of any kind concerning hybrids.

The Examiner also refers to column 3, lines 7-10 of Khosla '290 as allegedly teaching methods that are useful for "efficiently producing both new and known polyketides, using recombinant technology". The cited statement is silent as to types of PKS, as well as the very concept of hybrids, and certainly does not identically disclose or describe Applicants' claimed invention.

Finally, the Examiner contends that Khosla '290 is replete with teachings of hybrid (typeI) modular PKS genes and enzymes, referring to four specific passages in the paragraph bridging pages 17-18 of the May 21 Official Action. Column 4, lines 44-65 of Khosla '290 was extensively discussed in Applicants' previous response at pages 47-49. Taking this passage at face value, it concerns a method involving

recombination between first and second modules. Second modules are derived from "a pool of donor plasmids containing a random assortment of second modules of a modular PKS gene cluster". The expression "second modules of a PKS gene cluster evidently implies that all of the "second modules" referred to come from the same PKS. By contrast, Applicants' claim 1 requires a construct which is "heterologous".

The passage appearing at column 9, lines 38-50, of Khosla '290 is in a section headed "Definitions", which is not part of the disclosure of the invention itself, as discussed in Applicants' preceding response. In any case, there is no disclosure of a typeI/typeI hybrid gene cluster in the cited passage.

As for column 13, lines 53-58 of Khosla '290, this is an extremely broad description in the section headed "General Methods". It states that various host cells, which have just been described, "can be transformed with one or more vectors, collectively encoding a functional PKS set, or a cocktail comprising a random assortment of PKS genes, modules, active sites or portions thereof. The vector(s) can include native or hybrid combinations of PKS subunits or cocktail components or mutants thereof". This disclosure is of a very general nature and certainly contains nothing pointing specifically to Applicants' typeI/typeI hybrids.

Lastly, column 25, lines 24-40, is a speculative passage about what might be achievable in the future. One

statement in this passage reads: "the combinatorial potential within these multi-enzyme systems could be considerably greater than that for aromatic PKSs". There is then a reference to some prior art concerning "primer units", which concludes: "recent studies have shown that modular PKSs have relaxed specificity for their starter units". That apparently points to producing variants without the need for genetic manipulation, merely by feeding with different primers. The passage continues: "the degree of β-ketoreduction following a condensation reaction can also be altered by genetic manipulation". It is not clear what kind of manipulation is intended. (Possibly this refers to WO93/13663 in which Katz et al. demonstrated the destructive mutation of a reductive loop domain. Clearly "manipulation" by merely destroying an existing activity is relatively straightforward.) Later it is stated at Column 27, lines 9-13: "modular PKS's also exhibit considerable variety with regards to the choice of extender units in each condensation cycle although it remains to be seen to what extent this property can be manipulated" (emphasis added). The underlined wording emphasizes that this passage is not a disclosure of things taught by Khosla '290; it is merely a non-specific wish list.

Furthermore, there are errors of fact in Khosla's discussion of the prior art. First, much of the described structural diversity of type I primer units is not demonstrated but simply inferred from the structures. This is revealed, for example, when it is stated that pipecolic acid is a primer unit

in typeI PKSs - it isn't - it is a terminator (rapamycin, FK506 etc.). It is further stated that typeI PKSs have relaxed specificity for their starters. This is based only on the erythromycin case, and this occurs only in vitro. In vivo, the amount of non-natural starter unit erythromycin is exceedingly small. As such, it is synthetically useless.

Even if Khosla '290 could be fairly interpreted as suggesting typeI/typeI hybrids of the type claimed herein (which Applicants vigorously dispute), this reference still fails as evidence of unpatentability in this case because it does not place Applicants' invention in the possession of the public. It has long been held that when a prior art reference is relied on to show or suggest that an invention purportedly disclosed therein is unpatentable, such reference must place the invention in the possession of the public. In re Brown, 141 USPQ 245 (C.C.P.A. 1964). An invention is not possessed by the public absent some known or obvious way to make it. In re Payne, 203 U.S.P.Q. 245 (C.C.P.A. 1979). These same principles are articulated in §2121.01 of the Manual of Patent Examining Procedure.

As a preliminary point in this regard, it is noted that at page 9 of the May 21, 2002 Official Action, the Examiner misstates Applicants' argument. Notwithstanding the Examiner's characterization of Applicants' position, Applicants are not arguing that Khosla '290 fails to enable hybrid clusters that include typeI and typeII PKSs. Rather, it is Applicants'

position that Khosla '290 does not provide disclosure that enables typeI/typeI hybrid clusters.

Apparently recognizing the deficiencies in the disclosure of Khosla '290 as to the making of typeI/typeI hybrid clusters, the Examiner now relies on Khosla '290 "in combination with the state of the art", as stated at pages 9, 10 and 11 of the May 21, 2002 Official Action. However, the Examiner has not identified the nature of the information available in the state of the art on which she is relying to justify this conclusion. United States Patent and Trademark Office practice permits reliance on secondary evidence, such as other patents or publications, in order to show public possession of a method of making the claimed invention, e.g. in cases wherein a single reference discloses every element of the invention (which is not this case). Cf. In re Donohue, 226 U.S.P.Q. 619, 629 (Fed. Cir. 1985). The Examiner has not followed this practice, but instead makes an oblique reference to the state of the art as a substitute for such secondary evidence. This is clearly improper. In re Lee, 61 U.S.P.Q. 1430, 1435 (Fed. Cir. 2002) (when the examiner relies on what is asserted to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record).

It is the examiner's burden to provide evidentiary support for any finding of unpatentability, whether it be under §102 or §103. *Ex parte* Kung, 17 U.S.P.Q. 1545 (P.T.O. B.P.A.I. 1990); *Ex parte* Wolters, 214 U.S.P.Q. 735 (P.T.O. Bd. Apps.

1979).

Applicants have no evidentiary burden on issues of patentability unless and until the PTO satisfies its initial burden of proof on such issues. Nevertheless, as the Examiner has brought up the subject of the state of the art, Applicants will volunteer their understanding of the state of the art insofar as concerns hybrid PKS genes. The state of the art before the present invention by applicants may be summarized as follows:

- various streptomyces cloning vectors
- typeII PKSs for a number of polyketides (actinorhodin, frenolicin, graniticin, tetracenomycin etc.)
- typeII/typeII hybrids made by mix-and-match, in many cases giving rise to complex mixtures
- roles of individual enzymes in typeII systems not fully understood (cf. misattribution of role of CLF enzyme)
- Genes of only two type I PKS systems fully disclosed: erythromycin (DEBS) and rapamycin (RAPS). The architecture and mode of operation apparently very different from typeII PKSs; significant differences between DEBS and RAPS. Repositioning of the TE domain of DEBS so that a truncated gene (DEBS1-TE) produces a truncated PKS which produces a truncated polyketide (e.g.

triketide lactone)

- no full disclosure of any other typeI PKS genes
- no understanding of the basis of selectivity for different malonyl CoA extender esters (or loading acids), or the basis of stereochemistry of ketoreduction or enoylreduction in typeI PKSs
- destructive mutations of DEBS genes to produce modified erythromycins (WO93/13663)
- no experiments conducted on typeI/typeI hybrids.

Khosla '290, considered in view of the foregoing state of the art, provides no guidance that would lead to the successful production of the typeI/typeI hybrids claimed by Applicants herein.

There is no dispute that Khosla '290 discloses and enables the production of "recombinant gene products <u>in typeII systems</u>. TypeI PKS genes and their products, by contrast, are exceedingly complex systems, much more so than the typeII systems in which Khosla '290 apparently produced recombinant gene products.

A typeII system uses a small number of enzymes. They are not necessarily linked together. They cannot be of high specificity, since each enzyme functions repeatedly, at each stage of polyketide chain growth. It is thus relatively unsurprising that (a) one enzyme activity can be swapped for a corresponding one from a different typeII system; and (b) an enzyme will function with an unnatural substrate.

A typeI system, on the other hand, is a vast, linked system in which each enzyme activity is located at a specific location, and acts on a single substrate. There was certainly no reason to believe, based on Khosla '290 (with or without consideration of the state of the art) that simply replacing a gene encoding one activity would yield a multienzyme array that would be functional at all. An equally likely outcome, based on the knowledge then available, could have been that changing one part of the long protein chain might disrupt the conformation, destroying activity of other portions and/or disrupting the docking together of the giant proteins (such as DEBS1, DEBS2 and DEBS3 - see Fig. 2a), which are essential for a growing polyketide chain to be passed on. Even if unaffected by such generalized disruption, the 'replacement' enzyme activity would be presented with an unfamiliar substrate.

At the priority date of Khosla '290, the only typeI PKS gene cluster that had been sequenced was the erythromycin PKS. Thus, Khosla '290 cannot reasonably be interpreted as disclosing a system with parts "derived from at least two different modular PKS", as such a system is not enabled by Khosla '290. Certainly, there is no disclosure in Khosla '290 of any examples of the typeI/typeI hybrids claimed herein. There are likewise no examples of the corresponding claimed methods, which involve homologous recombination.

The Examiner comments at page 9 of the May 21, 2002 Official Action that Khosla et al. "have enabled the construction

and use of hybrid PKS gene clusters, since these are merely recombinant gene products". If this view held sway at the U.S. Patent and Trademark Office, few, if any, patents would be granted on advances in recombinant DNA technology, as most such advances involve "merely recombinant gene products". To suggest that Applicants' hybrid PKS gene is merely a recombinant gene product plainly begs the question, which is whether Applicants' claimed invention satisfies the statutory requirements of novelty, non-obviousness and utility/operability. On the present record, this question must be answered in the affirmative.

For all of the foregoing reasons, Khosla '290 does not constitute evidence of unpatentability with respect to the present invention. Therefore, the prior art rejections of claims 1-3, 25, 26, 31-37, 39, 44, 47, 49 and 55-58 based on Khosla '290 are untenable and should be withdrawn.

B. The 35 U.S.C. §103 Rejection of Claim 27 Based on Khosla '290 and Kao and of Claim 51 Based on Khosla '290 and Cox Cannot be Maintained

The obviousness rejection of claim 27, based on the combined disclosures of Khosla '290 and Kao, and of claim 51, based on the combined disclosures of Khosla '290 and Cox are improper for at least the same reasons cited above with respect to the anticipation/obviousness rejection of claims 1-3, 25, 26, 31-37, 39, 44, 47, 49 and 55-58 based on Khosla '290, alone. The citation of the Kao and Cox references fails to compensate for the above-noted, fundamental deficiencies of Khosla '290, with

respect to the failure to identically disclose or describe applicants' typeI/typeI PKS hybrids and to provide enabling methodology for the production thereof. That being the case, the §103 rejections of claim 27 based on Khosla '290 and Kao and of claim 51, based on Khosla '290 and Cox are untenable and should be withdrawn.

C. The Present Specification Satisfies the Written Description Requirement of 35 U.S.C. §112, First Paragraph with Respect to the Subject Matter of Claims 50 and 52-54, As Amended

The relevant inquiry in determining compliance with the written description requirement of 35 U.S.C. §112, first paragraph, is whether the originally filed specification reasonably conveys to a person having ordinary skill in the art, that, as of the application filing date, applicants had possession of the claimed subject matter. In re Kaslow, 217 U.S.P.Q. 1089 (Fed. Cir. 1983).

Furthermore, the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in applicants' specification disclosure a description of the invention defined by the claims. Ex parte Sorenson, 3 U.S.P.Q. 2d 1462 (Bd. Pat. App. 1987).

Claims 50 and 53 as originally presented, were drawn to a plasmid comprising a hybrid polyketide synthase gene according to claim 1 and an "int" sequence. The patentable aspect of claims 50 and 53 is the hybrid polyketide synthase gene of claim 1. There is nothing unique about the "int" sequence of

integration plasmids. The meaning of the term "int" sequence ("int" being short for integration) is well understood by those skilled in the art as evidenced by its appearance in standard student text-books since at least as early as 1988. The mere mention of the term is sufficient for anyone skilled in the art to know exactly what is intended. Exhibit A, which is submitted herewith, comprise copies of pages from the text book, Biochemistry by Lubert Stryer, 859-61 (1988), which clearly establish that "int" is a term of art. See also E. Winnacker, From Gene to Clone - Introduction to Gene Technology, at 153-54 (1987), a copy of which is attached as Exhibit B. By analogy, use of the term "int" sequence is similar to talking about "phenols" or "Grignard reagents" to a chemist. Although claims 52 and 53 are believed to be in compliance with the written description of 35 U.S.C. §112 as originally presented, they nevertheless have been amended to delete the terminology deemed objectionable by the Examiner with a view toward advancing prosecution of this application.

Claim 52, as amended, satisfies the written description requirement of §112, as it is clearly based on the specification as originally filed. Applicants' specification provides unequivocal evidence that applicants possessed the subject matter recited in claim 52, as noted above.

Regarding claim 54, there is a clear written description of this claim appearing at page 7, lines 29-35 of the specification. Moreover, as disclosed at page 3, lines 9-16, the

complete DNA sequence of the gene from S. hygroscopicus that encodes the modular Type I PKS governing the biosynthesis of rapamycin has been reported in the literature, and the sequence itself is available in EMBL/Genbank. That being the case, it necessarily follows that applicants' original specification reasonably conveys to those skilled in the art that applicants had possession of the subject matter of claim 54 as of their application's filing dated.

For the reasons stated above, the present specification clearly satisfies the written description requirement of 35 U.S.C. §112, with respect to the subject matter of claims 50 and 52-54. Thus, in view of the Examiner's failure to satisfy the United States Patent and Trademark Office's burden of proof with respect to the lack of written description rejection, as applied to the subject matter of claims 50 and 52-54, this ground of rejection should be withdrawn.

D. The Specification is Enabling with Respect to the Subject Matter of Claim 39, as Amended

The Examiner's reason for continuing to reject claim 39 is inapplicable in view of the present amendment of claim 39, which now calls for a method of making a polyketide by culturing the microorganism of claim 27, in which the microorganism is actinomycete. It is noted in this connection that S. lividans is included in new claim 59, which depends directly from claim 39 and which is supported by the disclosure at page 16, line 19 of the specification. This is an organism which does not

natively produce any known polyketide. However, Hutchinson et al., Ann Rev. Microbal., 49, 201-38 (1995) and Wang, Chinese J. Biotech., 5(4):261-69 (1989) describe its transformation to produce polyketides (see page 224, lines 5-6 of Hutchinson; and see English Abstract, last four lines of Wang). Copies of these literature references are enclosed as Exhibits C and D.

There can be no lingering dispute that the present specification, considered in light of the prior art at the time the present invention was made, is adequate to enable the full scope of claim 39. Accordingly, the 35 U.S.C. §112, first paragraph rejection of claim 39 is improper and should be withdrawn.

E. Claims 35 and 47 Should be Not be Subject to a Double Patenting Rejection in View of the Difference in Scope Between Them

The Examiner's assertion regarding the lack of clarity between the terms "plasmid" and "vector" is not understood. While it can be said that the term "plasmid" is often interchangeable with vector, it cannot be said that all vectors contain the features of a plasmid. For example, retroviral and adenoviral vectors are often capable of infecting and entering cells and would not be considered "plasmids" by the skilled person. Clearly, there is a difference in scope between the two terms which renders claims 35 and 47 patentably distinct.

In view of the present amendments and the foregoing remarks, it is respectfully urged that the objections and

rejections set forth in the May 21, 2002 Official Action be withdrawn and that this application be passed to issue and such action is earnestly solicited.

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Enclosures: Exhibits A-D

MARKED-UP VERSION OF AMENDED SPECIFICATION

For the PCR amplification for plasmid pKSA, [the following synthetic oligonucleotides were used as mutagenic primers, one containing a PstI site and the other a HindIII site: 5' -GATGGCCTGCAGGCTGCCCGGCGGTGTGAGCA- 3' (SEQ ID NO: 50) For the PCR amplification for plasmid pKSA,] the following synthetic oligonucleotides were used as mutagenic primers, one containing a PstI site and the other a HindIII site: 5′ -GATGGCCTGCAGGCTGCCCGGCGGTGTGAGCA- 3′ (SEQ ID NO: 50) and 5′ -GCCGAAGCTTGAGACCCCCGCCCGGCGCGGTCGC- 3′ (SEQ ID NO: 51)

MARKED-UP VERSION OF AMENDED CLAIMS

39. (Twice Amended) A method of making a polyketide by culturing the microorganism of claim 27 wherein said microorganism is an actinomycete.

50. (Amended) A plasmid comprising a gene according to claim 1 [and an int sequence whereby it] which is adapted to integrate into a specific attachment site (att) of a host's chromosome.

52. (Amended) A method of producing a transformant microorganism comprising the steps of:

(a) producing a plasmid which comprises donor DNA which encodes at least one domain of a first type I PKS;

(b) transforming with said plasmid an organism having a chromosome including PKS genes comprising at least one second type I PKS gene which is heterologous to said first PKS, [said plasmid and chromosome being mutually adapted so that] under conditions causing integration of said donor DNA [is integrated] into the chromosome so as to form with a portion of said second type I PKS gene a hybrid PKS gene encoding at least one domain of said first type I PKS and at least one domain of said second type I PKS.

53. (Amended) A method according to claim 51, wherein said plasmid is adapted to integrate into [includes an int

sequence and said chromosome has an] a specific att site [for integration of the] of said chromosome, said plasmid being integrated into said chromosome at a location suitable for producing said hybrid PKS gene.

54. (Amended) A hybrid PKS gene according to claim 1, wherein said first type I PKS naturally includes a thioesterase as a chain terminating enzyme, and wherein said hybrid gene includes a nucleic acid sequence encoding the enzyme from the rapamycin system which, in [that] said rapamycin system, effects connection of the polyketide chain to an amino acid chain in place of said thioesterase.